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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,246	12/11/2006	Takashi Okada	OKAD3006/GAD	6540

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EXAMINER	
KOSAR, ANDREW D	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,246	OKADA ET AL.	
	Examiner	Art Unit	
	ANDREW D. KOSAR	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-9 and 12-14* is/are rejected.

7)☒ Claim(s) *4-6,10,11 and 15-19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 December 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

Claims 4-6, 10, 11 and 15-19 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiply dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 3 describes the location of the gene transfer, however the independent claim is to a product with an intended use, and thus claim 3 does not limit the product claims.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:
Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 12-14 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-14 provide for the use of the HDACi, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Here, the claims are drawn to 'use of', but do not expressly provide any step, and appear to be drawn to a method of making the medicament.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless –
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 7-9 are rejected under 35 U.S.C. 102(a) as being anticipated by GOLDSMITH (M.E. Goldsmith et al. Clin. Cancer Res. (2003) 9, pages 5394-5401).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Goldsmith teaches FK228 (aka depsipeptide, FR901228) "preferentially enhances adenovirus transgene expression in malignant cells" (e.g. Title). Goldsmith concludes that they, "demonstrated that nontoxic doses of FK228, a HDAC inhibitor, can result in marked increases in expression of CAR and α_v integrin in cancer cell lines, whereas having little effect on cultured normal cells. These increases mediated enhanced transgene expression after adenovirus infection in cancer cell lines but not in cultured normal cells. These studies suggest a simple, clinically practical method for increasing the sensitivity of tumor cells to adenoviral gene therapy vectors, whereas potentially reducing unwanted toxicity in patients." (page 5399).

Claims 1-3 and 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by JUNG (M. Jung. Current Med. Chem. (2001) 8, 150—1511).

Jung teaches FR901228 (instant claim 2 compound) "has already entered clinical trials due to its impressive preclinical anticancer activity when it was discovered to be an inhibitor of HDAC in the low nanomolar range." (page 1508). Here, administration of the HDAC inherently increases the gene transfer efficiency.

Claims 1, 3, 7 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by KWON (H. J. Kwon et al. Int. J. Cancer (2002) 97, pages 290-296).

Kwon teaches that FK228 (formerly FR901228) "potently inhibited angiogenesis both *in vitro* and *in vivo*. FK228 induced the gene expression of angiogenic-inhibitory factors but suppressed that of angiogenic-stimulating factors, suggesting that the antiangiogenic activity of FK228 was derived fro the regulation of gene expression via the inhibition of HDAC activity." (page 290). Kwon teaches that "FK228, MS-27-275 and TSA are in clinical trial as an

antimelanoma, antirenal or antileukemia drug." (page 295). Here, administration of the HDAC inherently increases the gene transfer efficiency.

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by CHEN (IDS 2/1/06).

Chen teaches the use of HDAC inhibitors to reverse the silencing of virally transduced genes (throughout). Chen teaches that Trichostatin A and Butyrate, both HDAC inhibitors (throughout), "dramatically reactivates transgene expression." (page 5803).

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by KITAZONO (IDS 2/1/06).

Kitazono teaches FK228 enhances adenovirus transgene expression in malignant cells (e.g. Title), and showed efficacy in several cell lines- FTC235, SW-1736, HepG2, SW620, MCF7 and A498 (e.g. Figures 1-3, page 6329). Kitazono further teaches that "Previous studies done in our laboratory indicated that the addition of histone deacetylase inhibitors after trasnfection increase transgene expression of transiently transfected DNA. The addition of histone deacetylase inhibitors after adenovirus infection is known to increase the expression of viral proteins and transgene expression." (page 6329).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over KITAZONO, *supra*.

The teachings of Kitazono are presented above. Kitazono further teaches that "These studies suggest that FR901228 increases the efficiency of adenoviral transgene expression and may be useful in cancer gene therapy." (Abstract). "Preliminary results from our laboratory indicated that expression of proteins required for adenovirus infection might be increased by the histone deacetylase inhibitor FR901228." (page 6328). "These studies demonstrated that FR901228 increased CAR and α_v integrin RNA levels and resulted in marked enhancement of transgene expression after adenovirus infection." (page 6329). "In summary, we have demonstrated that nontoxic doses of FR901228, a histone deacetylase inhibitor, can result in marked increases in expression of CAR and α_v integrin in cancer cells. This increase mediates enhanced transgene expression after adenovirus infection. These studies suggest a simple, clinically practical method for increasing the sensitivity of tumor cells in adenoviral gene therapy vectors." (page 6330).

The difference between the instant claims and the teachings of Kitazono are that the instant claims are drawn to administering to a subject, while Kitazono is drawn to an *in vitro* method.

It would have been obvious to have practiced the method of Kitazono *in vivo*, as Kitazono states that the study suggests "a simple, clinically practical method for increasing the sensitivity of tumor cells in adenoviral gene therapy vectors." One would have been motivated to have done so, with a reasonable expectation for success in enhancing gene transfer efficiency, as Kitazono explicitly states that FR901228 functions as such *in vitro* and states that such *in vivo* method is suggested as being "a simple, clinically practical method" and that "these studies suggest that FR901228 increases the efficiency of adenoviral transgene expression and may be useful in gene therapy."

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANDREW D. KOSAR whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Andrew D Kosar/
Primary Examiner, Art Unit 1654